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EXAMINER	
LAM, ANN Y	

ART UNIT	PAPER NUMBER
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	09/927,779	ROUKES ET AL.	
	Examiner	Art Unit	
	Ann Y. Lam	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 33-60* is/are pending in the application.

4a) Of the above claim(s) *6-10, 33, 38, 39, 41-45, 48, 51, 52, 54-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,11-26,34-37,40,42,46,47,49,50 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/20/07*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement filed February 20, 2007 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. (Foreign Patent document JP 9-189701 does not have a translation of the document or the abstract and thus has not been considered.)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1-5, 11-13, 15, 17-26, 34, 35, 37, 40, 42, 46, 47, 49 and 50 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altmann et al., 6,545,492, in view of Thundat et al., 6,289,717.

As to claims 1, 34, 53, Altmann et al. disclose a receptacle (110) holding a sample (col. 16, lines 4-8), deemed to be the claimed solution reservoir. Altman et al.

also disclose that it is possible to bind sensing molecules to an AFM tip or to colloidal fields attached to an AFM cantilever and the molecules bound to the AFM probe can then be used as chemical sensors to detect forces between molecules on the tip and target molecules on a surface, allowing extremely high-sensitivity chemical sensing (col. 16, lines 12-17.) Altman et al. also teach that similarly, one may tailor AFM probes to sense, specific biological reactions, and for example [detect] the binding forces of individual ligand-receptor pairs. For example, one could bind DNA to a sample surface, on the one hand, and to a spherical probe attached to an AFM cantilever, on the other (col. 16, lines 18-26.) Altman et al. also teach that "[f]or all measurement situations in which the measurement results depend on the distance of the respective local probe of a sample, the principles of the present invention which allow independent measurement of the distance can be used advantageously" (col. 16, lines 29-33.) Moreover, Altman et al. teach that "[m]ore generally, in any local probing technique in which well-defined local measurement conditions are desirable, the principles of the present invention which allow stabilization of these local measurement conditions on the basis of measurement data referring to local measurements effected by at least one other local probe can be used advantageously" (col. 16, lines 33-39.)

Moreover, Altman et al. teach that instead of an oscillation of the cantilever by external driving, one can also use the thermal noise, i.e., thermal position fluctuations of the cantilever, to obtain information about the interaction between the cantilever and the sample surface (col. 17, lines 40-44) and from the measurement data, a number of parameters characterizing the thermally induced vibrations of the cantilever may be

calculated, for example a resonance frequency and a damping coefficient. (col. 16, lines 50-53.) The determination of the damping coefficient is the determination of damping of resonance motion claimed by Applicants. While the general disclosure of this embodiment, teaching the measurement of a damping coefficient, does not disclose molecules on the cantilever or on the substrate, Altman et al. teach that such measurements, i.e., using molecules on the cantilever and on the substrate in order to detect the forces between the molecules, can advantageously use this embodiment because it was specifically taught that "[f]or all measurement situations in which the measurement results depend on the distance of the respective local probe of a sample," or "[m]ore generally, in any local probing technique in which well-defined local measurement conditions are desirable", the principles of the present invention can be used advantageously (col. 16, lines 29-39.) That is, Altman et al. teach the use of the principles of the disclosed invention in probing techniques such as those involving measuring of molecular binding events. Alternatively, Altman et al. suggest the use of the principles of the disclosed invention in probing techniques such as those involving measuring of molecular binding events. That is, while the embodiment wherein it is taught that a damping coefficient can be measured does not disclose molecules on the substrate or on the cantilever, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize this embodiment in the measurement of interactions between molecules on a cantilever and on a substrate because such measurement results depend on the distance of the respective local probe of a sample and is a local probing technique in which well-defined local measurement conditions are

desirable, and it is taught by Altman et al. that "[f]or all measurement situations in which the measurement results depend on the distance of the respective local probe of a sample," or "[m]ore generally, in any local probing technique in which well-defined local measurement conditions are desirable", the principles of the present invention can be used advantageously (col. 16, lines 29-39.)

Moreover, Altman et al. teach that the resonator (cantilever) is disposed within the reservoir (110), (see fig. 1 and col. 16, lines 4-6, disclosing a sample within the receptacle; and col. 16, lines 65-67, disclosing interaction between the sample and cantilever tip near the sample surface.)

Altman et al. also disclose a detector in signal communication with the at least one resonator (40 and 42, col. 13, line 58.)

However, Altman et al. teach that the damping coefficient is a calculated parameter derived from the measurement data (col. 17, lines 50-53) rather than a detector that detects the damping coefficient. That is, there is no disclosure as to whether the calculation of the damping coefficient is performed by the detector, e.g., a microprocessor that is part of the detector, or whether it is calculated by human activity.

However, Thundat et al. teach a microprocessor for analyzing deflection information from the measuring steps in the use of a microcantilever (col. 6, lines 64-67.) Thundat et al. teach that "[w]ell known microprocessors and mathematical formulas are used to calculate the deflection changes as a function of specific target and detector molecular binding (col. 7, lines 6-9.) It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a microprocessor as taught by

Thundat et al. as part of the detector in the Altman et al. invention because Thundat et al. teach that such a microprocessor provides the benefit of performing mathematical formulas to calculate parameters from the measuring steps in the use of a microcantilever. The skilled artisan would recognize the benefits of a microprocessor as taught by Thundat et al. in calculating the derived damping coefficient from the measurement data in the Altman et al. invention.

Moreover, Altmann et al. however do not teach that the resonator is on the nanometer scale.

Thundat et al., however, teach microcantilevers as small as 1 micrometer wide, 1 micrometer long, and 0.3 micrometers thick (column 3, lines 54-60), which would therefore be on the nanometer scale (see for example claim 17, which depends from claim 1, reciting up to 1 micrometer in dimension.) Thundat et al. further teach that the resulting small size of the sensor require only minute concentrations of antigen to be used as the detecting molecule, allowing screening protocols to be developed for antigens or like detector molecules which are only available in limited supplies (column 7, lines 57-62).

It would have been obvious to have microcantilevers as small as 1 micrometer wide, 1 micrometer long, and 0.3 micrometers thick as the resonator of Altmann et al., as suggested by Thundat et al. because Thundate et al. teach that such small dimensions provide the benefit of requiring only minute concentrations of antigen to be used as the detecting molecule, allowing screening protocols to be developed for antigens or like detector molecules which are only available in limited supplies.

As to claim 2, Altmann et al. disclose that the at least one resonator comprises a vibrational resonator ("vibrating cantilever", col. 17, lines 50-53).

As to claim 3, the vibrational resonator ("vibrating cantilever", col.17, line 50-53) of Altmann et al. has a triangular notch at the base (see fig. 2), and therefore would be a notched vibrational resonator.

As to claim 4, Altmann et al. disclose that the at least one resonator is biofunctionalized with a receptor (col. 16, lines 17-39.)

As to claims 5, 42, Altmann et al. disclose that the device further comprises a substrate (i.e., surface of bottom of 110, see fig. 1 and col. 16, lines 4-6) disposed within the reservoir and adjacent to the at least one resonator (col. 17, lines 41-44 and col. 17, line 64 – col. 18, line 8), wherein the substrate is biofunctionalized with a ligand capable of molecular interaction with the receptor (see col. 16, lines 23-27, teaching that "one could bind DNA to a sample surface.... and to a spherical probe attached to an AFM cantilever".)

With respect to claim 11, Altman et al. do not teach that the resonator is made from silicon. However, Thundat et al. disclose that the microcantilever is preferably constructed of materials such as silicon or silicon dioxide which provides a useful substrate for the attachment of an antibody (column 4, lines 1-5). It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize silicon or silicon dioxide as the materials for forming the Altman et al. microcantilever because Thundat et al. teach that such materials provide the benefit of being useful as

a substrate for attachment of an antibody, as would be desirable in the Altman et al. microcantilever, which also may have molecules for detection of binding.

As to claim 12, Altmann et al. disclose that the detector is integral with the resonator (col. 14, lines 50-57, where piezo-electrical cantilevers that produces its own electrical signals for measurements of interactions with the sample is used.)

As to claim 13, Altmann et al. disclose that the detector is a piezoresistive transducer (column 13, lines 58-61).

As to claim 15, Altmann et al. disclose that the detector is an optical detector (col. 14, lines 56-60).

With respect to claims 17, 35, Thundat et al. teach microcantilevers as small as 1 micrometer wide, 1 micrometer long, and 0.3 micrometers thick (column 3, lines 54-60).

As to claims 18-22, Altmann et al. do not disclose that the resonator has a resonance motion vacuum frequency between about 0.1 and 12 MHz (claim 18), nor a force constant between about 0.1mN/m and 1N/m (claim 19), nor a Reynolds number between about 0.001 and 2.0 (claim 20), nor a mass loading coefficient between about 0.3 and 11 (claim 21), nor a force sensitivity of about $8fN/\sqrt{Hz}$ or greater (claim 22).

However, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233. In this case, Altmann et al. disclose the general conditions of the claims (see above with respect to claim 1), and the ranges recited in claims 18 through 22 relate to optimum or workable ranges and thus would only involve routine skill in the art according to *In re Aller*.

As to claims 23, Altmann et al. disclose that the resonator is biofunctionalized to detect a receptor/ligand interaction (col. 16, lines 16-39).

As to claims 24, Altmann et al. disclose that the resonator is biofunctionalized to detect DNA hybridization (col. 16, lines 16-39, particularly lines 23-25.)

As to claim 25, Altmann et al. disclose that the resonator is biofunctionalized to detect a chemical bond (col.8, lines 58-63).

As to claim 26, Altmann et al. disclose that the resonator is biofunctionalized to detect protein unfolding (col. 8, lines 58-60).

As to claim 37, Altmann et al. disclose a solution reservoir (110, see fig. 1); at least one biofunctionalized mechanical resonator disposed within the reservoir (see fig. 1 and col. 16, lines 4-6, disclosing a sample within the receptacle; and col. 16, lines 65-67, disclosing interaction between the sample and cantilever tip near the sample surface); a substrate (surface of the bottom of 110, see fig. 1) disposed within the reservoir and adjacent to the at least one resonator, wherein the substrate is biofunctionalized with a ligand capable of molecular interaction with the receptor ("one could bind DNA to a sample surface.... and to a spherical probe attached to an AFM cantilever"; col. 16, lines 23-27); and a detector capable of measuring a mechanical displacement of the resonator (40 and 42; see also col. 17, lines 32-36, and lines 45-47).

As to claim 40, Altmann et al. disclose that the substrate (surface of bottom of 110) is disposed in the reservoir (fig.1).

As to claim 42, Altmann et al. disclose that the substrate is biofunctionalized with a ligand and the resonator is biofunctionalized with a receptor ("one could bind DNA to a sample surface.... and to a spherical probe attached to an AFM cantilever" col. 16, lines 23-27; "molecules bound to the AFM probe can be used as chemical sensors to detect forces between the molecules on the tip and target molecules on a surface... for example, the binding forces of individual ligand-receptor pairs" col. 16, lines 14-20).

As to claim 46, Altman et al. disclose a driving element as claimed (see col. 17, lines 30-33, disclosing that the cantilever is externally driven to oscillate at a certain frequency.)

As to claims 47 (and thus its dependent claim 50), Altman et al. do not teach that a third receptor or third ligand in a solution binds to both a first receptor or ligand on the resonator and a second receptor or ligand on the substrate. However, Thundat et al. teach linkers that are compatible with the detector molecule to be used can be coated on the microcantilever, such linkers being for example poly-L-lysine which may also serve as stress transducers (col. 4, lines 10-14.) It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a linker such as poly-L-lysine on the Altman et al. microcantilever because Thundat et al. teach that it provides the benefits of serving as a linker for the detector molecules as well as a stress transducer. As to a detector for measuring a mechanical displacement of the resonator, Altman et al. teach this in column 17, lines 29-32 and 45-47.

As to claim 49, Altman et al. teach a piezo-electrical cantilever in column 14, lines 50-57, and thus a piezoresistive detector layer is considered to be located on the resonator.

2. Claims 14 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altmann et al., 6,545,492, in view of Thundat et al., 6,289,717, as applied to claim 13, and further in view of Chui et al., "Independent detection of vertical and lateral forces with a sidewall-implanted dual-axis piezoresistive cantilever", Applied Physics Letters, Vol. 72, Number 11, March 1998, pp. 1388-1390.

Altmann et al. in view of Thundat et al. teach a piezoresistive transducer, but do not teach that the transducer is made of p+doped silicon, as recited in claim 14, or that the transducer comprises a piezoresistive detector layer located on the resonator, as recited in claim 36.

Chui et al., however, teach a cantilever having a piezoresistive boron doped (p doped) layer (page 1388, fig. 1) on a silicon layer (page 1389, left column). Chiu et al. further teach that a piezoresistive boron layer provides high conductivity for detection of forces (see page. 1388, right column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to form the Altman et al.-Thundat et al. piezoresistive transducer from a boron doped layer on a silicon layer as taught by Chiu et al. because Chui et al.

teach that such material provides the advantage of high conductivity for detection of forces.

3. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Altmann et al., 6,545,492, in view of Thundat et al., 6,289,717, as applied to claim 1, and further in view of Lee et al., 5,807,758.

Altmann et al. in view of Thundat et al. teach a detector, as discussed above, but do not teach a lock-in detector.

Lee et al., however, teach a lock-in detector comprising piezoresistive elements directed through a pair of high pass filters and then into a lock-in amplifier (column 9, lines 11-25). Lee et al. further teach that lock-in techniques may be used to further reduce or eliminate noise by narrowing the bandwidth of the system (column 8, lines 65-67).

It would have been obvious to one of ordinary skill in the art to utilize the lock-in detector taught by Lee et al. as the detector of Altman et al. because Lee et al. teach that it provides the advantages of further reducing or eliminating noise by narrowing the bandwidth of the system.

Response to Arguments

Applicants' arguments have been considered but do not overcome the art of record. Applicants argue that Altman et al. do not teach or suggest measuring damping

of resonance motion. Applicants pointed out that column 17, lines 32-36 of the Altman et al. reference is not teaching measuring damping of resonance motion, which is a decay of the vibration amplitude versus time. Examiner finds this persuasive and notes that Examiner inadvertently pointed to column 17, lines 32-36 when column 17, lines 40-53 should have been cited. The new grounds for rejection now points to column 17, lines 40-53, which discloses that a damping coefficient can be calculated from the measurement data.

Applicants also argue that the method described in column 17, lines 15-28 and illustrated in figure 4b of Altman et al. involves the use of a biofunctionalized cantilever to perform intra-molecular force spectroscopy measurements but the tension forces acting on the cantilever are recorded, and there is no oscillation of the cantilever and there is no teaching of measuring a damping of resonance motion of the resonator. The teaching of Altman et al. relied upon by Examiner for teaching measuring a damping of resonance motion however is not in column 17, lines 15-28, but column 17, lines 40-53 as indicated above.

Applicants also assert that in the method described in column 17, lines 29-38 and illustrated in figure 4c, the cantilever is oscillated at a given frequency to obtain information about the interaction between the cantilever and the substrate and that this is a typical atomic force (AFM) microscopy method in which a scanned, oscillating cantilever AFM probe is used to image a surface of the substrate. Applicants assert that in this method however there is no molecular binding event between the cantilever and a biomolecule but that the distance between the cantilever and the substrate is

measured. Applicants assert that the cantilever is not biofunctionalized and there are no molecular binding events on the cantilever that are being measured, and thus this method does not provide measurement of damping motion in response to a molecular binding event on the resonator because there is no molecular binding event on the cantilever.

Examiner agrees that the disclosure in column 17, lines 29-38 does not specifically describe measurement of interactions between molecules. Lines 33-37 states "[t]he interactions between the oscillating cantilever and the sample, in particular, the sample surface, lead to a dependency of the oscillating amplitude of the distance. This dependency can be evaluated to obtain information about the interactions." Altman et al. do not specifically state in lines 29-38 that this embodiment measures molecular binding event.

However, in column 16, lines 12-17, Altman et al. disclose that it is possible to bind sensing molecules to an AFM tip or to colloidal fields attached to an AFM cantilever and the molecules bound to the AFM probe can then be used as chemical sensors to detect forces between molecules on the tip and target molecules on a surface, allowing extremely high-sensitivity chemical sensing. Altman et al. also teach that similarly, one may tailor AFM probes to sense, specific biological reactions, and for example [detect] the binding forces of individual ligand-receptor pairs. For example, one could bind DNA to a sample surface, on the one hand, and to a spherical probe attached to an AFM cantilever, on the other (col. 16, lines 18-26.) Altman et al. also teach that "[f]or all measurement situations in which the measurement results depend on the distance of

the respective local probe of a sample, the principles of the present invention which allow independent measurement of the distance can be used advantageously" (col. 16, lines 29-33.) Moreover, Altman et al. teach that "[m]ore generally, in any local probing technique in which well-defined local measurement conditions are desirable, the principles of the present invention which allow stabilization of these local measurement conditions on the basis of measurement data referring to local measurements effected by at least one other local probe can be used advantageously" (col. 16, lines 33-39.)

While the general disclosure of the embodiment in column 16, lines 12-17, does not disclose molecules on the cantilever or on the substrate, Altman et al. teach that measurements, i.e., using molecules on the cantilever and on the substrate in order to detect the forces between the molecules, can advantageously use this embodiment because it was specifically taught that "[f]or all measurement situations in which the measurement results depend on the distance of the respective local probe of a sample," or "[m]ore generally, in any local probing technique in which well-defined local measurement conditions are desirable", the principles of the invention disclosed by Altman et al. can be used advantageously (col. 16, lines 29-39.) Thus, Altman et al. teach or at least suggest the use of the principles of the disclosed invention in probing techniques such as those involving measuring of molecular binding events.

The teaching of detecting the damping of resonance motion is in column 17, lines 45-53. For the same reasons as stated above, Altman et al. teach or at least suggest the use of the principles of the disclosed invention, such as that in column 17, lines 45-

53, in probing techniques such as those involving measuring of molecular binding events.

As to claim 47, Examiner agrees with Applicants that Altman et al. do not teach the third receptor or ligand in solution. This deficiency has been cured in the new grounds of rejections above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

3/4/07

ANN YEN LAM
PATENT EXAMINER